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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,054	04/27/2006	Pieter Johan Peeters	PRD-2009-USPCT1	9048

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/11/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/533,054	PEETERS ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 33-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 33-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5 and 33-36 are pending and are examined on the merits.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/02/2010 has been entered.

This Office Action is in reply to Applicants' correspondence of 07/02/2010.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5 and 33-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The rejected claims are broadly drawn to methods for diagnosing depression or stress modulated by CRH induced gene expression, where the methods comprise determining a level of transcription of a gene comprising SEQ ID NO: 19.

The claims encompass the analysis of any subject organism.

The claims encompass the analysis of gene expression in any tissue sample.

The claims encompass the analysis of any analyte in the determination of a transcription level.

The claims encompass using any level of gene expression, and any comparison to any control, in the diagnosis of depression or stress.

The nature of the claimed invention thus requires knowledge of a robust and reliable correlation between a wide variety of gene expression levels in different sample types from any subject organism and the presence of a wide variety of phenotypes that are considered depression or stress.

Direction provided by the specification and working example

The instant specification teaches (p.40) an analysis of gene expression in a transgenic (TG) mouse model overexpressing corticotropin-releasing factor (CRF-OE) as compared to a wild type (WT) mouse. The specification provides that portions of several brains from different animals (p.41-Sample preparation) were used to prepare

RNA for mRNA expression analysis via array hybridization (p.41-Microarray hybridization). Relevant to the Election of SEQ ID NO: 19, Table 1 of the specification provides that the Hsd11b1 gene comprises SEQ ID NO: 19 and asserts that the gene is downregulated in the TG animals; and Fig 4 provides an analysis of Hsd11b1 expression analyzed by RT-PCR in hippocampus samples.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to determining the level of any particular transcription product is high, the unpredictability associated with correlating any compared level with a particular phenotype such as depression or stress is higher. Such unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

Because the claims encompass the analysis of biomarkers from any subject organism, whereas the instant specification provides only an anlysis of human subjects, it is relevant to point out the unpredictability in extrapolating gene expression results among different organisms. Such unpredictability is exemplified by Hoshikawa et al (2003), which teaches the analysis of gene expression in lung tissue in response to hypoxic conditions which lead to pulmonary hypertension (Fig. 1). The reference teaches that the gene expression profile in mouse is different from that observed in rat (Tables 1-4; p.209 - Abstract). Thus it is unpredictable as to whether or not any genes that are asserted to be related to stress in, for example, mouse are in fact applicable to predicting stress in any other non-mouse organism.

Because the claims encompass the analysis of gene expression in any tissue sample, whereas the instant specification provides the analysis of only particular brain samples, it is relevant to point out the unpredictability in extrapolating gene expression results among different tissue types. Such unpredictability is exemplified by Akil et al (US PG Pub 2006/0257903 A1), wherein Table 1 indicates that HLA-DPA1 is down-regulated in CB and nAcc brain tissues, but not in AnCg, DLPFC, PC or STG. Table 4 does not indicate any significance in HLA-DPA1 expression in lymphocytes, and the data of Tables 7 and 13 (indicating significance in expression of HLA-DPA1 for SZ, BP, and MDD in DLPFC) is not supported by Table 1 (where Table 1 indicates no significant changes in HLA-DPA1 expression in DLPFC for SZ). Such unpredictability is also demonstrated by Cobb et al (2002), which teaches the unpredictability in analysis of gene expression in spleen and liver sample from septic mice. Notably, Cobb et al teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., lns.2-8). Similarly p.48 lns.15-21 of the instant specification teaches the unpredictability in extrapolating gene expression results among different brain tissues.

Because the claims encompass any analyte in the measure of gene expression (e.g.: claim 35 is specifically drawn to immunological techniques, indicating protein analysis), while the specification teaches only the analysis of Hsd11b1 mRNA levels in TG and WT mouse brains, it is relevant to point out that other measures of gene expression do not always correlate with mRNA levels. For example, Chen et al (2002)

teaches that it is typical for protein abundances to not be correlated with mRNA abundances in tissue samples. It is thus unpredictable as to whether or not any non-mRNA analyte would in fact be predicative of mRNA expression.

Further, because the claims encompass the use of any level of gene expression compared to any control for the detection of depression or any stress it is relevant to point out the unpredictability associated with gene expression comparisons. For example, Cheung et al (2003; IDS of 06/10/2008) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). And Shalon et al (2001) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (PG Pub US 2001/0051344 p.10 ¶156, ¶158). The teachings of Cheung et al and Shalon et al are particularly relevant in light of the teachings of the specification (e.g.: p.42) which provide that analysis of gene expression was performed in only 3 or 4 samples subjects.

Finally, it is relevant to consider the breadth of the claimed methods in diagnosing stress or depression, where the actual analysis of the specification was performed with a transgenic mouse model. As such, any gene expression variations are relevant only to mouse subject with a life long exposure to CRH (p.46 lns. 11-13), and not necessarily indicative of acute stress or depression.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to perform large case:cotnrol analyses to determine the any level of Hsd11b1 gene expression, as compared to any control level, is in fact diagnostic of any stress or depression. Such experimentation would be required for any organism, of interest, and in any tissue, as encompassed by the claims. Even if such experimentation were to be performed, there is no assurance that the association asserted in the specification would be repeated and shown to be robust and reliable.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st paragraph for non-enablement of the claimed methods. Applicants arguments (p.4-5 of the Remarks 07/02/2010) have been fully and carefully considered but are not persuasive to withdraw the rejection. Applicants have argued that it is known in the art that the CRH signaling network correlates to the development of depression/stress; and, with regard to the numerous reference the Examiner has provided as objective evidence of the unpredictability associated with gene expression:phenotype correlations, that it is unreasonable to generalize the studies of the cited references to the unrelated biological conditions such as depression/stress modulated by CRH expression. The Examiner maintains that the instantly claimed diagnostic methods require more than a notion that the required SEQ ID NO: 19 transcript is somehow associated with the CRH signaling network; the methods as claimed require knowledge of a robust and reliable relationship between measured gene expression and the broadly recited particular phenotypes of depression or stress. Furthermore, Applicants arguments against the relevance of the references cited in the rejection are not consonant with Applicants attempts to broadly claim methods that, for example, encompass the analysis of any subject organism, analysis of gene expression in any tissue sample, any determination of any transcription level as compared to any control, in the diagnosis of any form of depression or stress.

The rejection as set forth is **MAINTAINED**.

Conclusion

3. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634